

A confederacy of proteinases

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The demolition of large buildings can be accomplished by a single explosive agent destroying a single class of structural components, namely weight-bearing beams. Although the breakdown of tissues in disease has often been conceived to occur in an analogous manner, with a single proteinase degrading a single structural ECM protein, it has become clear that effective tissue destruction requires several proteinases acting on diverse substrates. For example, the destruction of articular cartilage in osteoarthritis involves the degradation of aggrecan, type II collagen, and other matrix components by many different enzymes produced by a variety of cell types (1). In this issue of the *JCI*, Longo et al. (2) extend this concept to vascular disease, reporting that aneurysm formation in mice requires the activity of at least two matrix metalloproteinases (MMPs), gelatinase-A (MMP-2) and gelatinase-B (MMP-9), released by different cell types.

The hallmark pathology of abdominal aortic aneurysms is the destruction of medial elastic lamellae. Because lamellae are the main structural component of large arteries, it is reasonable that their breakdown, coupled with continuous arterial pressure, would lead to vessel expansion and, eventually, rupture. Elastic lamellae are made principally of elastic fibers, and elastic

fibers are composed primarily of elastin, as well as microfibrillar and other proteins (3). Thus, elastases, the proteinases that can degrade elastin, have been targeted as the destructive agents in aneurysms. Of the various classes of elastases, the metallo-elastases are prominently expressed in human aneurysms and have been the most studied group of matrix-degrading proteinases in aneurysm research (4, 5). Indeed, animal studies provide compelling evidence that one class of MMP, the metallo-gelatinases (6), includes destructive agents important for the pathogenesis of aneurysm formation. Clinical studies are ongoing to assess the efficacy of MMP inhibitors in halting progression of asymptomatic aortic aneurysms (7).

Two years ago, Thompson and coworkers reported that aneurysm formation is blocked in gelatinase-B knock-out mice but not in macrophage metallo-elastase-deficient (MMP-12-deficient) mice (8). Using a slightly different model, Longo et al. (2) also find that aneurysms do not form in gelatinase-B-null deficient mice. Because gelatinase-B in aneurysms is a product of inflammatory cells, primarily macrophages (9), it is reassuring that both groups verified that inflammation in the injured aortic wall was not affected by a lack of this MMP. Both groups also restored aortic expansion in gelatinase-B-null mice with a bone marrow transplant from wild-type mice, thus demonstrating the importance of inflammatory cell-derived gelatinase-B. Longo et al. further showed that gelatinase-A-null mice do not develop aneurysms following aortic injury. In the vessel wall, as in most tissues, gelatinase-A is expressed primarily by resident mesenchymal cells, specifically medial smooth muscle cells (10). Indeed, bone marrow from wild-type

mice did not restore aneurysm formation in gelatinase-A knock-out mice (2). These are interesting findings, particularly to one with a proteinase-centric view of the world, since they suggest that the gelatinases act on different substrates. However, these data do not demonstrate that either gelatinase has degraded the elastin in the vessel wall.

As their name suggests, MMPs are thought to be responsible for the turnover and degradation of connective tissue proteins, a function clearly performed by several family members. However, matrix degradation is not the sole function of these enzymes. Several reports from recent years have suggest-

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ed or demonstrated that various MMPs can activate a variety of non-matrix proteins, including cytokines, chemokines, integrins, and antimicrobial peptides (11). Thus, MMPs should not be viewed solely as proteinases of ECM catabolism, but rather as extracellular processing enzymes involved in regulating cell-cell and cell-ECM signaling events (12, 13). With the current data from the aneurysm studies, one cannot conclude that the gelatinases degrade elastin or any other protein component of elastic lamellae. Clearly, the gelatinases are required for lamellar destruction in aneurysm formation in mice, but how they function, whether directly or indirectly, is unknown. The substrates they degrade or cleave in the artery wall remain unidentified. Of potential relevance to

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Nonstandard abbreviations used: matrix metalloproteinase (MMP); gelatinase-A (MMP-2); gelatinase-B (MMP-9); macrophage metallo-elastase (MMP-12).

elastolysis, gelatinase-B can provide cover for neutrophil elastase, a serine proteinase, by degrading its principal inhibitor, the serpin $\alpha 1$ proteinase inhibitor (14). Thus, gelatinases could mediate elastin breakdown by a gain-of-function mechanism rather than by directly degrading the matrix, a loss-of-function mechanism. Identifying the actual in vivo substrates of extracellular proteinases — not a straightforward task — is essential to understanding how these enzymes function and, as for the gelatinases in aneurysm formation, how they can conspire to cause devastating tissue destruction.

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